CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

DICLOFOP-METHYL

SB 950-237 tolerance # 385

November 25, 1986, Revised 5/19/93; 3/24/98

I. DATA GAP STATUS

Combined, rat:	No data gap, possible adverse effect.
Chronic, dog:	Data gap, inadequate study, no adverse effect indicated.
Oncogenicity, mouse:	Data gap, inadequate study, possible adverse effect indicated.
Reproduction, rat:	Data gap, inadequate studies, possible adverse effect indicated.
Teratology, rat:	No data gap, no adverse effects.
Teratology, rabbit:	Data gap, inadequate study, no adverse effect indicated.
Gene mutation:	No data gap, no adverse effect.
Chromosome effects:	No data gap, no adverse effect.
DNA damage:	No data gap, no adverse effect.
Neurotoxicity:	Not required at this time.

Note, Toxicology one-liners are attached

** indicates acceptable study
Bold face indicates possible adverse effect
File name T980324

Revised by T. Kellner, 5/19/93; M. Silva, 3/24/98.
Record numbers through 158126 (Doc. 385-096) have been examined.

These pages contain summaries only. Individual worksheets may contain additional effects.

II. TOXICOLOGY SUMMARY

COMBINED RAT

**** 096 158126** "Combined Chronic Toxicity (12 and 24 months) and Carcinogenicity (24 months) Study in Rats," (Ehling, G., and Donaubauer, H.H.; Hoechst Aktiengesellschaft, Pharma Development, Corporate Toxicology, D-65926 Frankfurt am Main; 1/8/96). Hoe 023408 (purity = 95.3%) was fed in diet to Hoe: WISKf(SPF71) rats (10/sex/dose-12 month sac.; 20/sex/dose-24 month chronic & 50/sex/dose-24 month carcinogenicity study) at 0, 4.5, 45 or 450 ppm. In addition, females were treated at 900 ppm (79 mg/kg/day) for 24 weeks. **Chronic NOEL = 4.5 ppm** (Body weight gains were significantly decreased in both sexes at 450 ppm. Mortality was excessive for females at 900 ppm. Both sexes showed hematological and clinical chemistry effects in the chronic and onco studies at $\geq$ 45 ppm (chronic). Females showed a decrease in urine volume and an increase in specific activity at 450 ppm. Livers and kidney of both sexes at $\geq$ 45 ppm showed a dark brown discoloration. In addition, males at 450 ppm showed liver enlargement after 12 & 24 months (chronic & onco). Small testes were observed in males at 450 ppm. Females showed enlargement of pituitary gland at 450 ppm (onco). Both sexes showed significantly increased absolute and/or relative liver weights at 450 ppm. Relative kidney weights were significantly increased in both sexes at $\geq$ 45 ppm. Absolute and relative spleen weights were significantly decreased at 450 ppm in both sexes and adrenal weights were also decreased in both sexes at 450 ppm. Liver showed severe hepatocellular enlargement at $\geq$ 45 ppm which was centrilobular in both sexes. It was also diffuse in males at 450 ppm. Males showed cholestasis at 450 ppm. Necrotic foci was observed at $\geq$ 45 ppm in males. Single cell foci and increased mitotic activity were also observed in male livers at $\geq$ 45 ppm. Brownish-yellow granular deposits were observed in liver parenchymal cells. Kidney tubule cells showed brownish-yellow granular deposits at $\geq$ 45 ppm. There was also an increase in focal tubular atrophy in both sexes at 450 ppm.) **Possible Adverse Effect:** Carcinogenicity NOEL = 45 ppm (There was an increase in liver adenomas--Males 0, 1, 0 14; Females 1, 0, 1, 6 and carcinomas--Males 0, 0, 0, 18; Females 1, 0, 3, 14 at 0, 4.5, 45 and 450 ppm. This incidence of adenomas and carcinomas was from both chronic and onco studies combined.) Acceptable. (M. Silva, 3/24/98).

026, 027 036123, -24, -25 and 036401 Title: Combined Chronic Toxicity and Tumorigenicity Study with Hoe 23408 O H AT003 in Rats after Dietary Administration for Two Years. (7/19/78, Hoechst, Report No. 449/78.) JR(G), 11/18/85. Diclofop-methyl, batch no. 18, [97% per 47081]; fed to SPF Wistar rats, 90/sex/group, at 0, 2.0, 6.3, or 20.0 ppm for two years; diets mixed weekly; NOEL > 20 ppm; incomplete (pages 496 - 3241 not included - missing individual data on pathology.); unacceptable (doses not justified and high dose is inadequate for chronic testing; no clinical observations.) No adverse effect reported.

Upon submission of the missing pages (47083 to 47101), the following comments are made: The 90-day subchronic study upon which the dose selection is based (or justified) has been reviewed. The subchronic (385-006, #31298) does not substantiate the selection of 20 ppm as the high dose. Analysis of diet was performed only once for stability. This does not assure appropriate mixing/levels over the duration of the study. No new histopathology is contained in the additional pages now submitted. Study is still UNACCEPTABLE (no analysis of diet, dose selection with inadequate high dose, histopathology presentation - not all animal numbers are included in the report.) No adverse chronic or oncogenic effect is reported. NOEL > 20 ppm.

EPA 1-liner: Guideline [Date of last update - 6/11/85.] Oncogenic NOEL > 20 ppm (HDT); Systemic NOEL > 20 ppm. Note: EPA graded the 90-day subchronic feeding study as minimum with a NOEL = 32 ppm. Doses tested were 0, 12.5, 32, 80 and 200/500 ppm.

035 to 048 047088 to 047101 (7/19/78, Hoechst.) JG, 10/17/86. Complete version of 36123, etc., with missing pages. See under 36123 above for comments. No change in status.

385-076 098216 [Addendum for -035:047088 to -048:047101] Leist, K. and Schollmeier, U. "Testing of HOE 023408 - Substance Technical (Code: HOE 023408 0H AT002) 90-day Feeding Study in SPF Wistar Rats" (Hoechst Report No. 90.0063, 2/23/90). Note: This report is a reformated version of 006:031298. This submission, along with the original version, provided range-finding data used to establish dose levels for the combined rat chronic/oncogenicity study. Diclofop-methyl technical (Code: Hoe 023408 0 H AT002), purity of 96%, was fed in the diet at 0 (control), 12.5, 32, 80 and 200/500 ppm (concentration was increased to 500 ppm 45 days into the study) to 20 immature SPF Wistar Rats/sex/dose for 90 days. Body weight gain was reduced in the high-dose group (about 10% lower) and microscopic examination showed dose-related centrilobular enlargement of liver cells from 80 ppm upwards. Relative liver weights were increased in the 80 and 200/500 ppm males and in the 32, 80 and 200/500 ppm females. Increases in SGOT, SGPT and AP were reported in the 80 and 200/500 ppm groups six to seven weeks into the study (increases reversible during 14-day recovery period). Clinical symptoms and general behavior showed no dose-related effects. The author concluded that the NOEL was 12.5 ppm (probably a conservative estimate) based on liver weight increases observed in the 32 ppm females. Kellner and Gee, 2/16/93.

034 047082 Response by Hoechst-Roussel to review of 36123, etc. JG, 10/21/86.

007, 009 025264, 025272 Interim reports for 36123, etc. JW, 6/26/85.

034 047081 Response by Hoechst-Roussel to review of 25264 and 25272. JG, 10/21/86. Purity of test article in rat study stated to be 97% with analysis attached, dated 12/10/75. The response points out that these two reports are interim to the final report at two years.

CHRONIC DOG

007 025265 Title: Report on a Repeated-Dose (15 Months) Oral Toxicity Study pf Hoe 23408 O H AT003 in Beagle Dogs. (8/17/77, Hoechst, Report No. 809/77.) Diclofop-methyl, [purity of 97% from 47084]. Beagle dogs were fed 0, 8, 25 or 80 ppm in the diet for 15 months; 6/sex/group; unacceptable with insufficient information for assessment (no analysis of diet or food consumption data, no individual histopathology/gross necropsy.) No mortality. Some effects on liver in females in high dose group: increased weight, fatty change in 4/6 females. Apparent NOEL = 8 ppm (fatty liver changes.) J. Wong, 6/26/85.

The response to the review, 385-034, 47084, contains summary tables of hematology, clinical chemistry and organ weights, making comparison of the dose groups easier. Study is still UNACCEPTABLE but POSSIBLY UPGRADEABLE with the submission of food consumption data and records showing diet preparation. Because diets were mixed daily, periodic sampling for analysis might not give an accurate estimate of the actual intake over the 15-month period. Liver effects are considered an indication that the high dose was marginally adequate.
EPA 1-liner: Minimum. NOEL = 8 ppm; (1/6 (F) - lymphosarcoma in small and large intestine, fatty liver deposits.)

034 047084. Response by Hoechst-Roussel to review of 25265. JG, 10/20/86. Purity of test article stated to be 97% with the diet mixed daily and "...No analysis was necessary." Status of study is not changed.

077, 034, 007 098220, 047084, and 025265 Brunk, R., et al. "Testing of HOE 023408 - Substance Technical (Code: HOE 023408 00 ZC98 0002) for Toxicity by Repeated Oral Administration (15 Month Feeding Study) to Beagle Dogs" (Pharma Research Toxicology and Pathology, Hoechst Aktiengesellschaft, Germany, Report # A 42775, January 24, 1990, **Note**: this is a reformatted version of record number 025265 that was originally dated 8/17/77 and reviewed by DPR on 6/26/85). Diclofop-methyl, 97% purity, was administered in the diet to 6 Beagle dogs/sex/group for 15 months at nominal concentrations of 0 (control), 8, 25, and 80 ppm. Increased liver weights in the high-dose group and fatty changes in the liver at 25 and 80 ppm were reported. Adverse effects were not indicated. Nominal chronic NOEL = 8 ppm. **Unacceptable, not upgradeable** (animals were not adequately challenged; no verification of test material content in feed mixture). Green, Kellner and Gee, 2/4/93.

385-076 098215 [Addendum to -077:098220]. Brunk, R. and Mayer, D. "Testing of HOE 023408 Technical (Code: HOE 023408 00 ZC98 0002) for Toxicity by Repeated Oral Administration (3 Month Feeding Study) to Beagle Dogs" (Hoechst Report No. 90.0102, 2/3/90). This report is a reformated version of 006:031299. This submission provided range-finding data used to establish dose levels in the chronic dog study -077:098220. Diclofop-methyl technical (Code: Hoe 023408 00 ZC97 0002) was fed in the diet at 0 (control), 80, 250 and 800 ppm to 4 Beagle dogs/sex/dose for 3 months. One high-dose animal was killed following the 30th administration (severe necrosis of the oral mucosa, gingiva and the lips); all remaining animals survived to the end of the test. High-dose dogs showed slightly reduced group mean body weight and pale, clay-colored liver with distinct lobular markings. Livers in this group showed significant weight increases. Two high-dose males showed very small testes (one of these males also showed small hemorrhagic fields on the cut surface of the the dorsal part of the prostate gland). Microscopic findings at 800 ppm included focal tubular atrophies in the renal cortex, urate crystal deposits, lipomatosis and destruction of myocardial fibers, hepatocellular steatosis, disturbance of hemopoiesis and spermatogenesis, increased content of lipids in the suprarenal cortex and phlogistic atrophy of the gastric mucosa. **NOEL = 250 ppm** (for body weight, clinical chemistry, hematology, liver function, organ weights and macroscopic findings). Kellner and Gee, 3/16/93.

ONCOGENICITY, MOUSE

028, 029, 030 036126, -27, -28, -29, -30, -31 Title: Toxicity and Tumorigenicity of Hoe 23408 O H AT003 in Mice during Dietary Administration for 2 Years. (7/19/78, Hoechst, Report No. 448/78.) JR(G), 11/19/85. Diclofop-methyl, Batch no. 18 [97% per 47083], fed for 102-104 weeks to 130/sex/test group and 260/sex in control at 0, 2, 6.3 or 20 ppm; 15/sex/group sacrificed at week 88; feed analysis data other than a one week stability assay not included; systemic NOEL = 2 ppm, onco NOEL = 6.3 ppm; unacceptable (justification of dose selection, no inventory of tissues actually examined for each animal, no individual clinical observations, inadequate analysis of diet); terminal organ weights increased at mid and high dose for liver and kidney; SAP increased in both sexes at high dose. The number of liver nodules was increased in the 20 ppm group, especially in males, and the significance is discussed by several pathologists. The nodules occurred against a background of toxic liver effects and may be an extension of the hyperplastic response. The overall incidence of benign and malignant tumors was, if anything, lower in the 20 ppm groups.

Submission of the missing pages in 47102 to 47111 does not change the review of

UNACCEPTABLE but the study is POSSIBLY UPGRADEABLE with the submission of the subchronic study on which dose selection was based and satisfactory data on diet preparation and analysis as well as the complete report of individual data.
EPA 1-liner: Guideline. Oncogenic NOEL = 6.3 ppm (benign liver tumors in males and females); Systemic NOEL = 2 ppm (increased kidney and liver weights in males and females, increased heart weight in males and increased SAP in males.)

049 to 056 047102 to 047111 (7/19/78, Hoechst.) JG, 10/17/86. More complete version of 036126 to 036131.

034 047083 Response by Hoechst-Roussel to review of 36126 to 31. JG, 10/23/86.

385-079 098234 [Addendum for -028:036126 to -030:036131 and 47102 to 47111] Leist, K., Mayer, D. and Schollmeier, U. "Testing of HOE 023408 - Substance Technical (Code: HOE 023408 0H AT003) Toxicity and Tumorigenicity Study in Mice during Dietary Administration for 2 Years with Interim Sacrifice after 88 Weeks" (Hoechst Report No. 90.0054, 7/19/78). Note: This report is a reformatted version of the report contained in vol. -028 to -030. This version contains a re-examination of histopathology with changes in the diagnoses of neoplastic and non-neoplastic findings together with historical control data (liver lesions) for Hoe:NMRKf/SPF71 male and female mice. Data from a 28-day feeding study to investigate the induction of hepatic enzymes in the NMRI mouse were included, in addition to recent data for dosing material analyses and citation of the 90-day rat feeding study (original report -006:031298, reformated version -076:098216) used to set dosing levels. **Possible Adverse Effect:** equivocal findings of liver adenoma and carcinoma at 20 ppm. **No status change**, the study remains **unacceptable**. Records of diet preparation and individual clinical observations were not included; complete histopathologic preparations and examinations were not performed on animals found dead or killed in extremis (by study termination, up to 65% of the animals per group fell into this category). Green, Kellner and Gee, 2/23/93.

023 49151, 49152, 982861, microscopic evaluation of liver nodules for 036126 through 36131.

REPRODUCTION, RODENT

008 025356 Title: Multigeneration Study with Hoe 23408 OH in Rats. (8/77, Central Inst. for Nutrition and Food Research, Report No. R 5446.) JW, 6/26/85. Diclofop-methyl, 98.0%; 10 male rats and 20 female Wistar rats were fed 0, 10, 30 or 100 ppm; 3 generations, 2 litters per generation; 7 deaths at high dose; UNACCEPTABLE (inadequate necropsy - not all animals; no individual necropsy/histopathology data, no analysis of diet, mating procedure of groups of 5 males with 10 females - if this is correct.) Decreased birth weight and growth during lactation with increased mortality of pups at high dose. Apparent reproductive NOEL = 30 ppm; maternal NOEL > 100 ppm.
EPA 1-liner: Minimum. NOEL = 30 ppm (increased pup mortality.)

034 047080 Response by Hoechst-Roussel to review of 25356. JG, 10/20/86. No change in status for 025356.

385-081 111214 Osterburg, I. "Diclofop-Methyl; Substance Technical (Code: HOE 023408 OH ZD93 0002), Two Generation Oral (Dietary Administration) Reproduction Toxicity Study in the Rat (One Litter per Generation)", (Hazleton Laboratories, Deutschland GmbH, HLD Project No. 169-023,

August 1991). Diclofop-methyl (batch CO 7278067, 93% purity) was administered in the diet to 2 generations (1 litter/generation) of 25 parental Sprague Dawley Crl: CD (SD)BR rats/sex/group at 0 (control), 10, 30, and 100 ppm. Adult rats were treated for 14 weeks prior to mating and continued to be treated during gestation and lactation. Increased absolute and relative liver and kidney weights as well as microscopic changes (eg. cellular hypertrophy and functional swelling of the nucleus of hepatocytes in the liver) were reported in both sexes of high-dose F0 and F1 parental animals; kidney findings included hyaline casts, calcified deposits in the medulla and/or pelvis, and yellow-brown pigment deposits in the convoluted tubules (intracytoplasmic). **Parental NOEL ≥ 30 ppm.** Changes noted in F1a and/or F2a pups included decreased survival, reduced body weight, retarded physical development, decreased absolute spleen, kidney and testicular weight and increased absolute liver weight. Microscopic findings included cellular hypertrophy and functional swelling of the nucleus of hepatocytes in the liver and calcified deposits in the medulla of the kidney. **Possible Adverse Effect:** Reduced number of pups born alive, reduced pup weight, retarded pup development and focal testicular atrophy (F1a) at 100 ppm. Reproductive NOEL = 30 ppm. **Unacceptable**; possibly upgradeable with rationale for dose level selection. Green, Kellner and Gee, 1/26/93.

385-083 118469 [Revised version of **385-081 111214**] Osterburg, I. "Diclofop-Methyl; Substance Technical (Code: HOE 023408 OH ZD93 0002), Two Generation Oral (Dietary Administration) Reproduction Toxicity Study in the Rat (One Litter per Generation)", (Hazleton Laboratories, Deutschland GmbH, HLD Project No. 169-023, August 1991). This report contains histopathological data from the low (10 ppm) and intermediate (30 ppm) dose groups (adults and pups) that were not included in -081:111214. The only additional finding was hepatocyte hypertrophy and hyperplasia in 30 ppm-dosed F1 adults. **No status change**; the study remains unacceptable, but upgradeable. Kellner and Gee, 5/17/93.

TERATOLOGY, RAT

**078, 007, 034 098222, 025268, 047078, "Testing for Embryotoxicity in the Wistar Rat after Oral Administration", (M. Albrecht, Dilp. Ing., et al, Pharma Research Toxicology and Pathology, Hoechst Aktiengesellschaft, Germany, 3/22/90). Note: This is a reformatted version of record 025268 (1/15/75). Reviews by DPR of the initial versions of this report resulted in unacceptable, upgradeable status. This latest version addresses some of the deficiencies (eg. individual clinical findings and maternal necropsy data) that were listed in these reviews. Necropsy data for 100 mg/kg dams found dead was not provided because of autolysis.

Diclofop-methyl, 96.0% purity was administered by gavage to 20 mated female Wistar rats WISKf(SPF71)/group on gestation days 7 through 16 at 0 (sesame oil), 10, 32, and 100 mg/kg/day. Reduction in body weight gain was reported in dams at 32 and 100 mg/kg/day and 12 of 20 dams died at 100 mg/kg/day between days 13 and 21 of gestation. Retarded growth, increased resorptions, and increased variants were noted in fetuses at 32 and 100 mg/kg/day. **Adverse effects were not indicated**. Maternal NOEL = 10 mg/kg/day (reduced body weights at the mid- and high-dose). Developmental NOEL = 10 mg/kg/day (retarded fetal growth, increased resorptions, and increased variants at 32 and 100 mg/kg/day). **Acceptable.** Wong, Parker, Green, Kellner and Gee, 2/8/93.

EPA 1-liner: Minimum. Teratogenic NOEL > 100 ppm (HDT), fetotoxic NOEL = 10 ppm (LDT) reduction in body weight, increased resorptions, dilatation of the renal pelvis or distension of the ureter); maternal NOEL < 10 ppm (LDT) (increased liver weights).

034 047078 Response of Hoechst-Roussel to review of 25268. Contains analysis of test article as 98% but analysis certificate numbers to not match with the report. JG, 10/24/86.

TERATOLOGY, RABBIT

032 036135 Title: Effect of Hoe 23408 O H AT003 on Pregnancy of the Rabbit, Strain Hoe: HIMK (SPFWiga) after Oral Administration. (4/26/78, Hoechst, Report No. 296/78.) JAP, 11/22/85. Diclofop-methyl, [97% per 47079 - note the analysis is dated 1975 and the study was conducted in 1977] given by oral gavage on days 7 - 19 of gestation to 15 rabbits per group at 0, 0.03, 0.3 or 3.0 mg/kg; maternal NOEL = 0.3 mg/kg (liver and kidney weights increased); developmental toxicity NOEL = 3.0 mg/kg (HDT); unacceptable and incomplete (no analysis of dosing solution, method or frequency of preparation; marginal evidence for maternal toxicity; inadequate number of fetuses examined - guidelines call for all fetuses for both skeletal and visceral defects, not 1/2 for each.) Conclusion reached is that study needs to be repeated with a sufficient number of fetuses examined. No indication of developmental toxicity is reported.
EPA 1-liner: Minimum. Teratogenic NOEL > 3.0 mg/kg/day (HDT); Maternal NOEL = 0.3 mg/kg/day (decreased food consumption and body weight and increased liver and kidney weights; fetotoxic NOEL > 3.0 mg/kg/day (HDT).

034 047079 Response by Hoechst-Roussel to review of 36135. JAP, 11/24/86.

-074 98209, Reformatted version of 36135. Albrecht, M. and Baeder C. "HOE 23408 Technical (Code: HOE 23408 OH AS204) Testing for Embryotoxicity in the Himalayan Rabbit after Oral Administration" (Hoechst Report No. 90.0264, 3/19/90). **No status change**; the study remains unacceptable and not upgradeable (no analyses of dosing solutions and inadequate number of fetuses examined). Kellner and Gee, 5/14/93.

MUTAGENICITY, GENE

Microbial systems

** 008 025271 (10/5/77, Hoechst.) JW, 6/26/85. Diclofop-methyl, no purity stated; Salmonella strains TA1535, TA1537, TA98 and TA100; with and without activation, duplicate plates, at 0.2, 2, 20, 500 or 5000 ug/plate. No evidence of increased reversion rate.
EPA 1-liner: Minimum. Negative at 5 mg/plate.

031 036132 Title: Study of the Mutagenic Activity in vitro of the Compound Hoe 23408 with Schizosaccharomyces pombe. (4/14/80, Instituto di Ricerche Biomediche.) JR(G), 11/19/85. Diclofop-methyl, 95.0%; tested in Schizosaccharomyces pombe with and without rat liver activation at 0, 250, 500 or 1000 ug/ml, for 4 hours; 12-16 plates/concentration; positive controls were MMS (-S9) and DMBA (+S9); no increase in mutant colonies in adenine operon; unacceptable (no repeat trial).
EPA 1-liner: Acceptable. Negative mutagen with and without activation.

034 047087 Response by Hoechst-Roussel to review of 36132 stating that the guidelines at the time the study was conducted did not require a repeat trial. In any case, the data gap is filled with study 25271.

Mammalian systems

075 098212 Muller, W. "Detection of Gene Mutations in Somatic Cells in Culture HGPRT-Test with V79 Cells" (Pharma Research Toxicology and Pathology, Hoechst Aktiengesellschaft, Germany, Report # A 36569, 7/6/87). Diclofop-methyl technical, 94.5% purity, was tested for mutagenic potential with and without metabolic activation (Aroclor 1254-induced rat liver S-9 fraction) at 0, 50, 100, 150, 200, 300, or 500 ug/ml using the HGPRT mutation assay (3 trials) with V79 Chinese hamster lung fibroblasts (4 hour exposure). **Increased mutation frequency is not indicated. **Acceptable**. (Green, Kellner and Gee, 2/2/93)

MUTAGENICITY, CHROMOSOME

075 098213 Muller W. "Evaluation of Hoe 023408 - Substance, Technical (HOE 23408 00 ZD93 0002) in the In Vivo Cytogenetic Test in Bone Marrow Cells of the Chinese Hamster-Chromosome Analysis-", (Pharma Research Toxicology and Pathology, Hoechst Aktiengesellschaft, Germany, Report # A43225, 4/2/90). Diclofop-methyl, 95.1% purity, was tested at 0 (sesame oil), 200, 1000, and 2000 mg/kg in the in vivo cytogenetics (chromosomal aberration) assay using 5 Han: Chin Chinese Hamsters/sex/dose level/sampling time (bone marrow was sampled at 12, 24, and 48 hours). **Increased chromosomal aberrations were not indicated. **Acceptable**. (Green, Kellner and Gee, 3/3/93).

075 098211, "Diclofop-Methyl, Substance Technical (code: HOE 023408 00 ZD95 0003), Study of the Capacity to Induce Chromosomal Aberrations in Human Lymphocytes Cultured in Vitro", (Dr. R. Pirovano, Pharma Research Toxicology and Pathology, Hoechst Aktiengesellschaft, Germany, Report # A36668, 9/9/87). Human male lymphocytes were treated with diclofop-methyl at concentrations of 0, 1, 10, 50, 100, and 500 ug/ml for 4 hours with and without metabolic activation (Aroclor 1254-induced rat liver S-9 fraction). **Chromosomal aberrations were not indicated. **Acceptable**. (Green, Kellner and Gee, 2/1/93)

008 025269 Title: Dominant-Lethal Test for Determination of Mutagenic Effect of Hoe 23408 O H AT003 in Male NMRI - Mice after Oral Administration. (5/9/77, Hoechst, Report No. 489/77.) JW, 6/27/85. Diclofop-methyl, [97% per 47086] dominant lethal in NMRI mice, 30 males per group; given 0, 10, 32 or 100 mg/kg by oral gavage, 5 daily doses; mated 1:1 for 12 4-day periods; initial low dose group discontinued due to failure of water supply and was replaced; UNACCEPTABLE (no concurrent control or historic data, doses not justified, - evaluated as insufficient information for independent assessment. No adverse effect reported.

The submission of a study with a positive effect conducted in 1972 (see 047113) as the positive control for a 1976 study (25269) is not acceptable.
EPA 1-liner: Minimum. Negative at 100 mg/kg (HDT).

034 047086 Response by Hoechst-Roussel to review of 25269. Purity of test article stated to be 97%.

056 047113 Duplicate of 25269 plus a dominant lethal study with thio-Tepa conducted in 1972 showing a positive effect in NMRI mice.

056 047114 Title: Dominant Lethal Assay with Hoe 23408 OH in Male Albino Rats. (Central Institut Voor Voedingsonderzoek, Report No. R 4869, 11/75). JG, 10/17/86. Diclofop-methyl (no purity statement, no lot number); given by oral intubation to 12 males/group at 0, 10 or 50

mg/kg/day, 5 days; MMS control; mated 1:2; increased mean number of dead implants at 50 mg/kg, weeks 1 through 5 with weeks 2 and 3 showing highest numbers. UNACCEPTABLE (characterization of test article, two doses only.)

SUMMARY: The dominant lethal studies conducted in two different labs give conflicting results. Neither one is acceptable and the issue of possible adverse effect cannot be resolved without submission of further data.

008 025270 Title: Testing of Hoe 23408 O H AT003 for Mutagenicity after Oral Administration to NMRI Mice - Micronucleus Test. (8/23/77, Hoechst.) JW, 6/27/85. Diclofop-methyl, [97% per 47085] micronucleus test in NMRI mice, 10/sex/group, given 0, 10, 32 or 100 mg/kg by oral gavage twice at 24 hour interval; sacrificed 6 hours after second dose; counted 2000 polychromatic erythrocytes per animal; no positive control included; analysed only 5/sex/group; UNACCEPTABLE (no positive control, single sacrifice time.) No adverse effect reported.

See 047112. Study 025270, 8/23/77, is unacceptable but negative (single sampling time - evidence now shows that more than one time should be sampled, including 24 hours, inadequate high dose for this test type, selection of 5 from a group of ten animals for analysis is not explained, positive control of cyclophosphamide not acceptable - this test was conducted 5 years after the test with diclofop-methyl.
EPA 1-liner: Minimum. Negative at 100 mg/kg/day (HDT).

056 047112 Duplicate of 025270 plus a report using cyclophosphamide for mouse micronucleus. JG, 10/17/86.

034 047085 Response by Hoechst-Roussel to review of 025270. Purity of test article stated to be 97%.

Document 385-034 contains a statement that a sister chromatid exchange assay is in progress and the report will be submitted when available.

MUTAGENICITY, DNA/OTHER

** 031 036134 (6/81, Litton Bionetics.) JR(G), 11/19/85. Diclofop-methyl, 94%; unscheduled DNA synthesis in primary hepatocytes; 0, 0.5, 1.0, 2.5, 5, 10, 25, 50 or 100 ug/ml, 18 hours; cytotoxicity at 100 ug/ml; triplicate samples, total of 150 cells/concentration, two trials; no increase in UDS is reported. Acceptable.
EPA 1-liner: Acceptable. Negative mutagen.

031 036133 (4/14/80, Instituto di Ricerche Biomediche.) JR(G), 11/19/85. Diclofop-methyl, 95.0%; Saccharomyces cerevisiae D4 strain tested with and without rat liver activation at 0, 250, 500 or 1000 ug/ml, 4 hours; 4 plates per concentration; unacceptable (high concentration not justified by cytotoxicity; only 4 of recommended 6 plates per concentration.)

NEUROTOXICITY

Not required at this time.